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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JL-23357-PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. **PCT/KR2004/002771**	International filing date *(day/month/year)* **30 OCTOBER 2004 (30.10.2004)**	Priority date *(day/month/year)* 30 OCTOBER 2003 (30.10.2003)

International Patent Classification (IPC) or national classification and IPC

C07D 501/22(2006.01)i

Applicant

CJ CORPORATION et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ (sent to the applicant and to the International Bureau) a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demamd	Date of completion of this report
11 MARCH 2005 (11.03.2005)	13 JANUARY 2006 (13.01.2006)
Name and mailing address of the IPEA/KR Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer KIM, Hee Jin Telephone No. 82-42-481-5412

Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/KR2004/002771

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☒ This report is based on translations from the original language into the following language English, which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☒ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this reort as "originally filed" and are not annexed to this report):*

   ☒ the international application as originally filed/furnished

   ☐ the description:
   pages _____ as originally filed/furnished
   pages* _____ received by this Authority on _____
   pages* _____ received by this Authority on _____

   ☐ the claims:
   pages _____ as originally filed/furnished
   pages* _____ as amended (together with any statment) under Article 19
   pages* _____ received by this Authority on _____
   pages* _____ received by this Authority on _____

   ☐ the drawings:
   pages _____ as originally filed/furnished
   pages* _____ received by this Authority on _____
   pages* _____ received by this Authority on _____

   ☐ the sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   ☐ the description, pages _____
   ☐ the claims, Nos. _____
   ☐ the drawings, sheets _____
   ☐ the sequence listing *(specify)* : _____
   ☐ any table(s) related to sequence listing *(specify)* : _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   ☐ the description, pages _____
   ☐ the claims, Nos. _____
   ☐ the drawings, sheets _____
   ☐ the sequence listing *(specify)*: _____
   ☐ any table(s) related to sequence listing *(specify)* : _____

** If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/KR2004/002771

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-6	YES
	Claims		NO
Inventive step (IS)	Claims	1-6	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-6	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents are referred to :

D1 : WO 02/68428 A1

D2 : WO 02/83692 A1

D3 : WO 03/11871 A2

D4 : The Journal of Antibiotics, 1987, 40(7), pp.991-1005

D5 : US 4699979

D1 discloses a preparation method of cephalosporin which comprises reacting a cephem compound with a 4-hydroxyphenylglycine whose carboxylic acid group is activated by pivaloyl chloride.

D2 discloses that 3-(Z)-propenyl cephem compound is selectively prepared by reacting phosphoranylidene cephem compound with actaldehyde in the presence of a base in a solvent mixture essentially comprising diethyl ether.

D3 discloses a process for the production of cefprozil (which is the same compound as the compound of formula 1 of the present invention) comprising reacting cephem compound of formula III in the form of an amidine salt with a mixed carboxylic acid anhydride of 4-hydroxyphenylglycine.

D4 describes the synthesis of BMY-28100 compound which is an 3-alkenyl derivative of 7-phenylglycyl cephalosporins. The synthetic scheme in D4 discloses that 7-amino-3-chloromethyl-3-cephem-4-carboxylate is acylated with N-BOC-protected phenylglycine in the presence of dicyclohexylcarbodiimide and Wittig reaction is performed with aldehyde in dichloromethane or chloroform in the presence of a base.

D5 discloses that the addition of lithium halide improves the proportion of Z/E isomer in Wittig reaction and acylation of 7-amino-3-propen-1-yl cephalosporin with N-BOC protected 4-hydroxyphenylglycine is carried out in the presence of dicylclohexylcarbodiimide as a coupling reagent.

(Continued on Supplemental Sheet)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Box V.

The present invention relates to a method of preparing cephalosporin compound of formula 1 comprising the steps of (a) reacting a phosphoranylidene cephem compound of formula (4) with acetaldehyde in the presence of a base in a solvent mixture comprising water, isopropanol and methylene chloride in the ratio of 1:3~6:11~14 to give compound of formula (3) and (b) acylation of the compound of formula (3) with 4-hydroxyphenylglycine derivative of formula (4).

1. Novelty and Inventive Step

None of the prior art suggests the solvent system claimed in the present invention for raising the Z- to E-isomer ratio in Wittig reaction.
Although D2 suggests a two-phase solvent system and the organic phase thereof essentially comprising a diethyl ether for raising the Z-isomer, D2 also describes that it is difficult to raise Z-isomer content to above 83% when using a conventional organic solvent such as methylene chloride. Therefore, it is not obvious to a skilled person seeking reaction condition for raising the Z-isomer content to apply the solvent system claimed in the present invention.
Although D1 also discloses a compound of formula (2) in the present invention as an activated derivative of 4-hydroxyphenylglycine for acylation, D1 is silent about the reaction condition for improving the Z-isomer content in Wittig reaction.
Therefore, the novelty and inventive step of the present invention can be acknowledged.

2. Industrial applicability

The present invention has industrial applicability.